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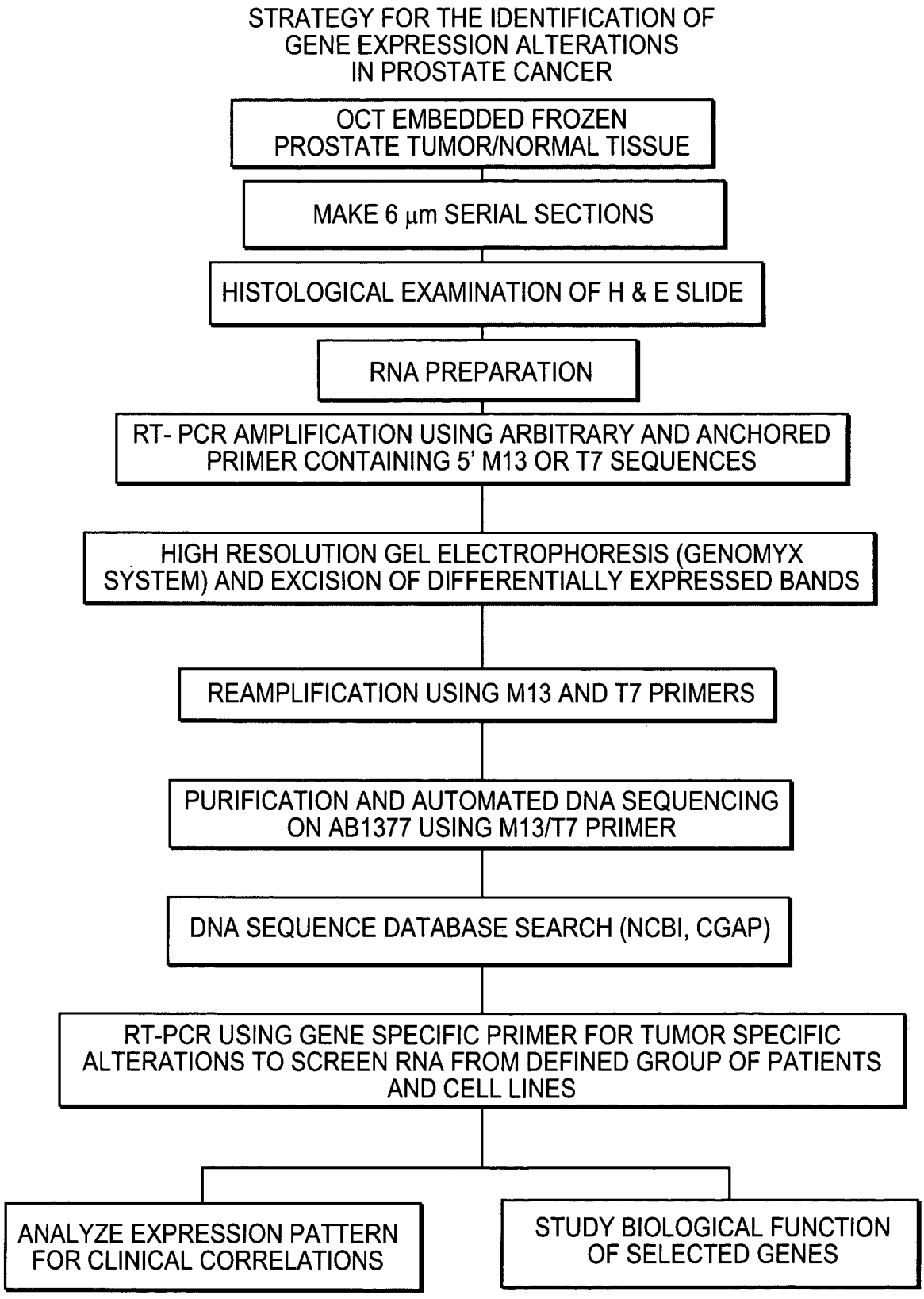
STRATEGY FOR THE IDENTIFICATION OF GENE EXPRESSION ALTERATIONS IN PROSTATE CANCER
OCT EMBEDDED FROZEN PROSTATE TUMOR/NORMAL TISSUE
MAKE 6 μm SERIAL SECTIONS
HISTOLOGICAL EXAMINATION OF H & E SLIDE
RNA PREPARATION
RT- PCR AMPLIFICATION USING ARBITRARY AND ANCHORED PRIMER CONTAINING 5' M13 OR T7 SEQUENCES
HIGH RESOLUTION GEL ELECTROPHORESIS (GENOMYX SYSTEM) AND EXCISION OF DIFFERENTIALLY EXPRESSED BANDS
REAMPLIFICATION USING M13 AND T7 PRIMERS
PURIFICATION AND AUTOMATED DNA SEQUENCING ON AB1377 USING M13/T7 PRIMER
DNA SEQUENCE DATABASE SEARCH (NCBI, CGAP)
RT-PCR USING GENE SPECIFIC PRIMER FOR TUMOR SPECIFIC ALTERATIONS TO SCREEN RNA FROM DEFINED GROUP OF PATIENTS AND CELL LINES
ANALYZE EXPRESSION PATTERN FOR CLINICAL CORRELATIONS
STUDY BIOLOGICAL FUNCTION OF SELECTED GENES

FIG. 1

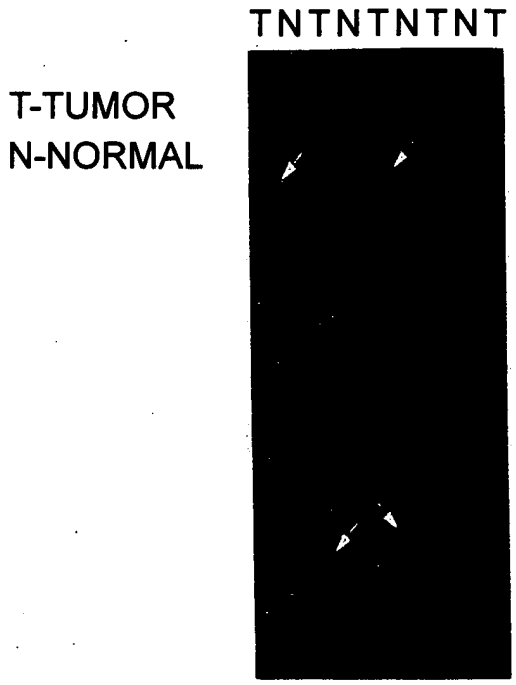
TNTNTNTNT
T-TUMOR
N-NORMAL

FIG. 2

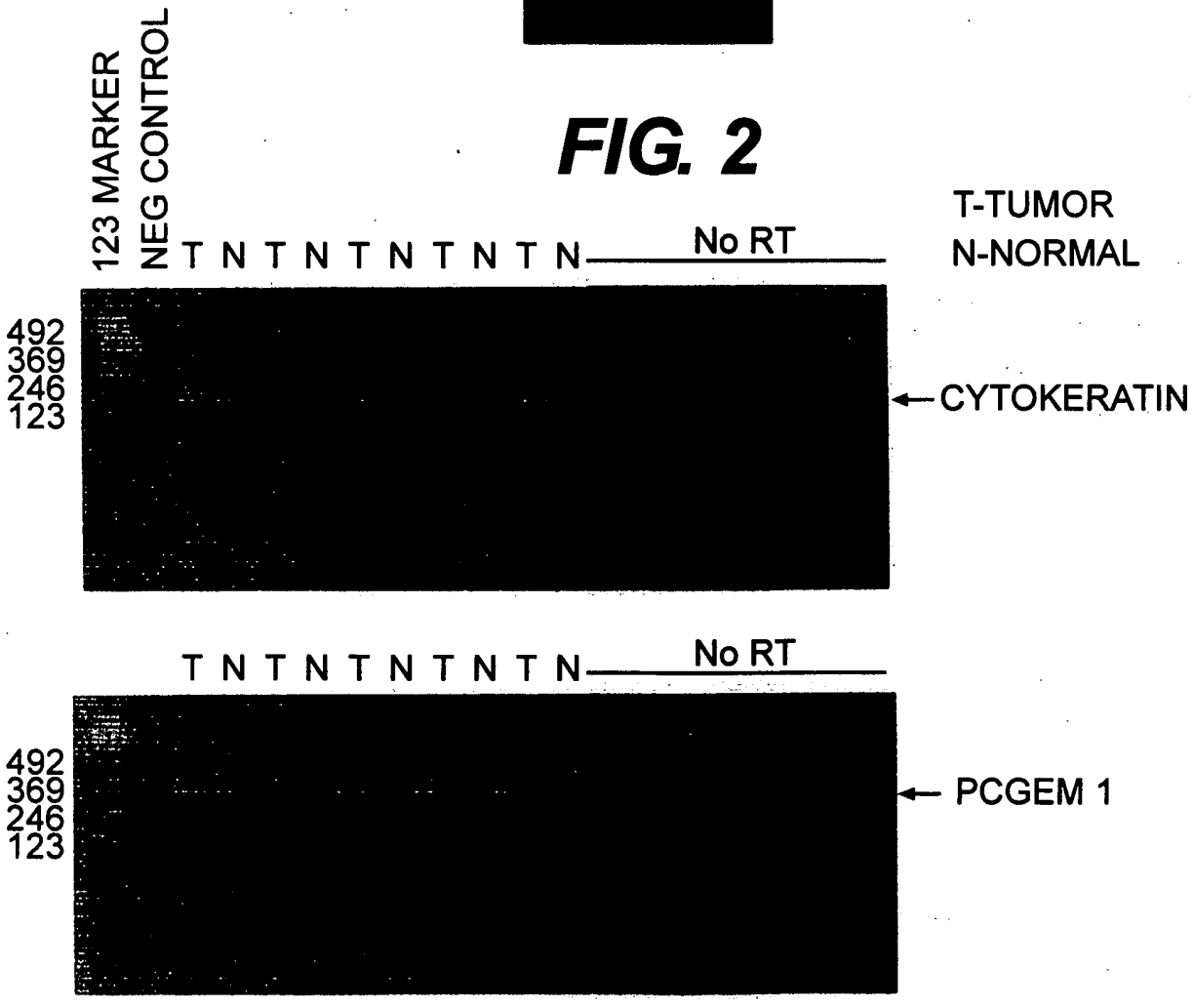
123 MARKER
NEG CONTROL
T N T N T N T N T N
No RT
T-TUMOR
N-NORMAL
492
369
246
123
CYTOKERATIN
T N T N T N T N T N
No RT
492
369
246
123
PCGEM 1

FIG. 3

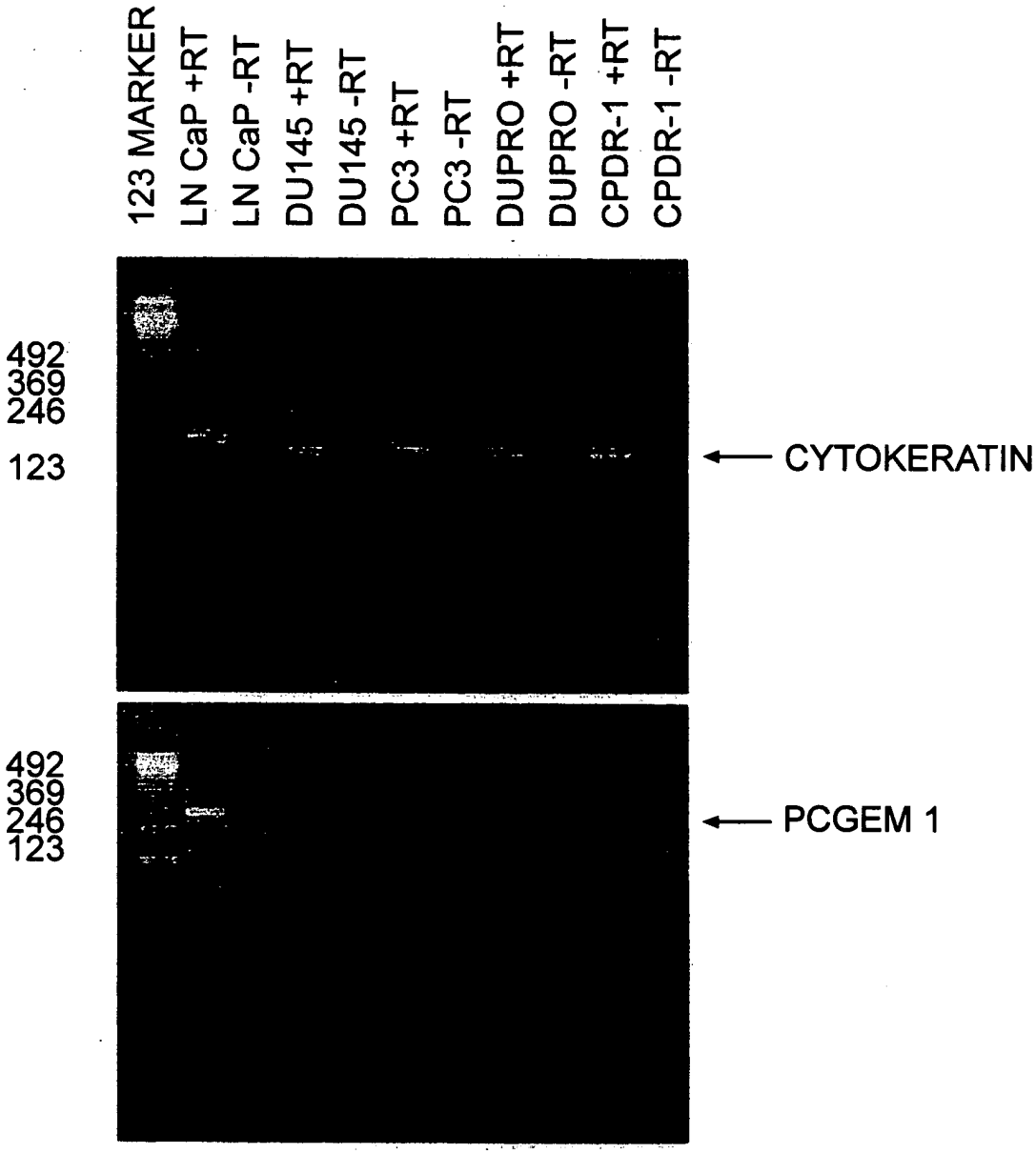
123 MARKER
LN CaP +RT
LN CaP -RT
DU145 +RT
DU145 -RT
PC3 +RT
PC3 -RT
DUPRO +RT
DUPRO -RT
CPDR-1 +RT
CPDR-1 -RT
492
369
246
123
CYTOKERATIN
492
369
246
123
PCGEM 1

FIG. 4

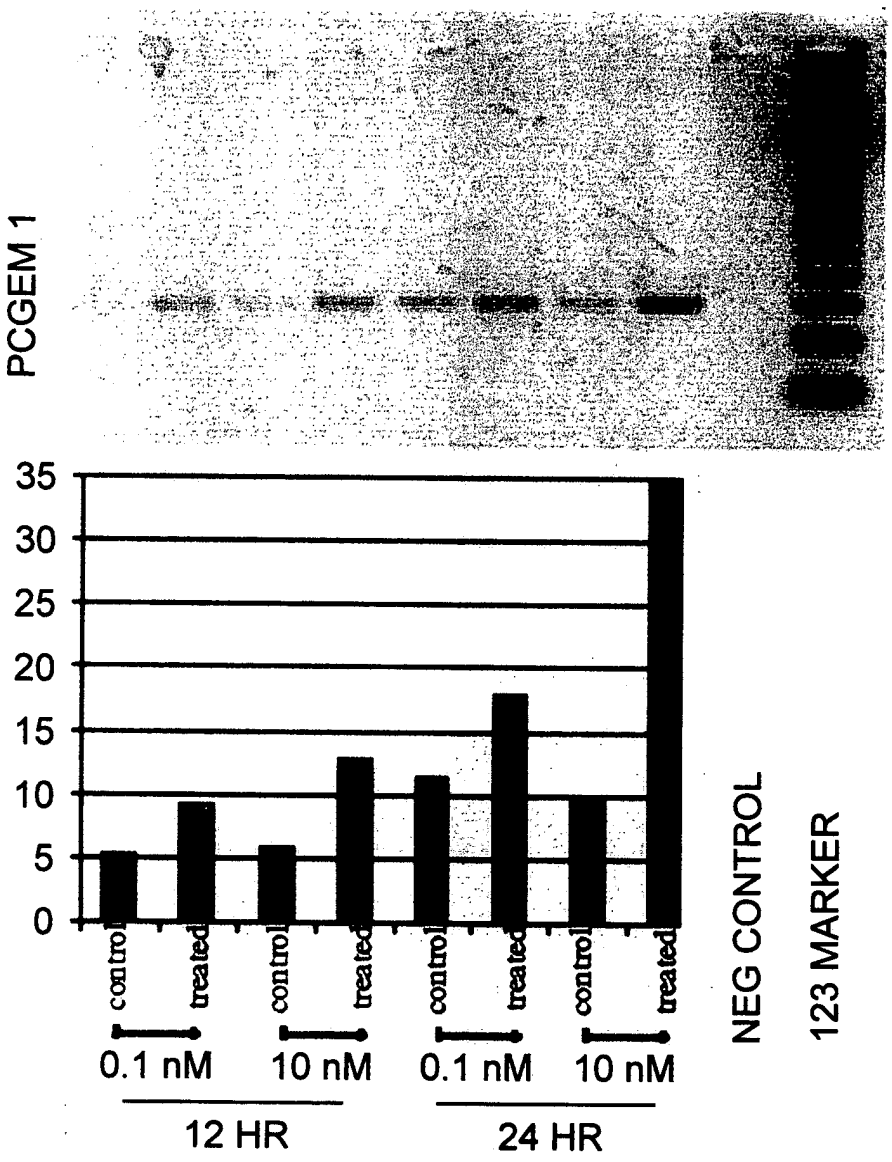
PCGEM 1
35
30
25
20
15
10
5
0
control
treated
control
treated
control
treated
control
treated
0.1 nM
10 nM
0.1 nM
10 nM
12 HR
24 HR
NEG CONTROL
123 MARKER

FIG. 5A

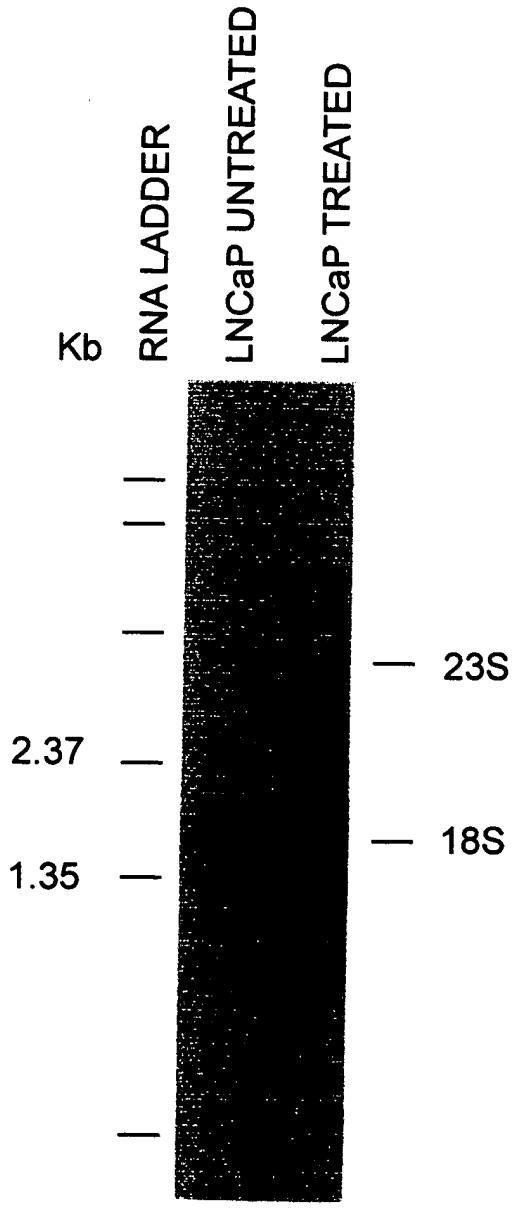

FIG. 5B

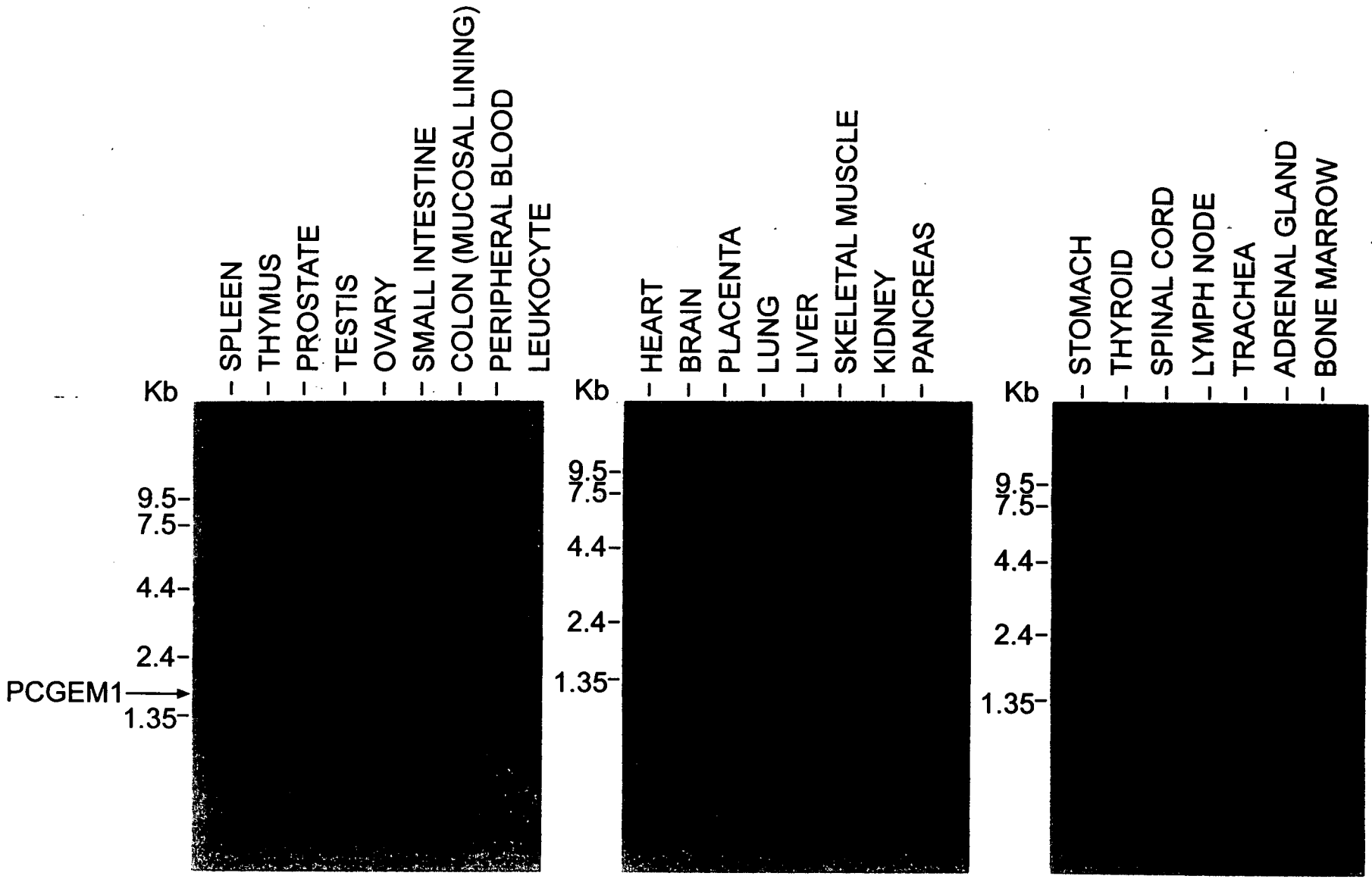
Kb
SPLEEN
THYMUS
PROSTATE
TESTIS
OVARY
SMALL INTESTINE
COLON (MUCOSAL LINING)
PERIPHERAL BLOOD
LEUKOCYTE
9.5
7.5
4.4
2.4
PCGEM1
1.35
Kb
HEART
BRAIN
PLACENTA
LUNG
LIVER
SKELETAL MUSCLE
KIDNEY
PANCREAS
9.5
7.5
4.4
2.4
1.35
Kb
STOMACH
THYROID
SPINAL CORD
LYMPH NODE
TRACHEA
ADRENAL GLAND
BONE MARROW
9.5
7.5
4.4
2.4
1.35

FIG. 6A

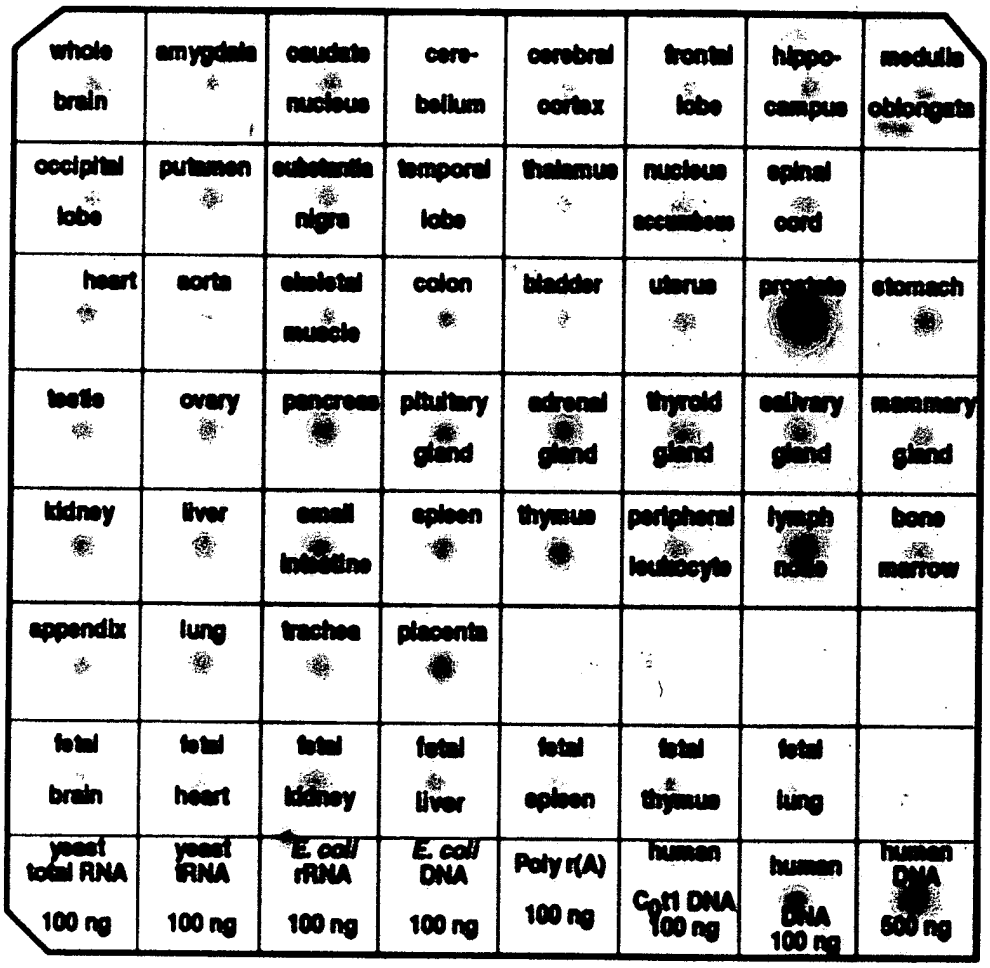
whole brain
amygdala
caudate nucleus
cere-bellum
cerebral cortex
frontal lobe
hippo-campus
medulla oblongata
occipital lobe
putamen
substantia nigra
temporal lobe
thalamus
nucleus accumbens
spinal cord
heart
aorta
skeletal muscle
colon
bladder
uterus
prostate
stomach
testis
ovary
pancreas
pituitary gland
adrenal gland
thyroid gland
salivary gland
mammary gland
kidney
liver
small intestine
spleen
thymus
peripheral leukocyte
lymph node
bone marrow
appendix
lung
trachea
placenta
fetal brain
fetal heart
fetal kidney
fetal liver
fetal spleen
fetal thymus
fetal lung
yeast total RNA 100 ng
yeast tRNA 100 ng
E. coli rRNA 100 ng
E. coli DNA 100 ng
Poly r(A) 100 ng
human Cot1 DNA 100 ng
human DNA 100 ng
human DNA 500 ng

FIG. 6B

FIG. 7A

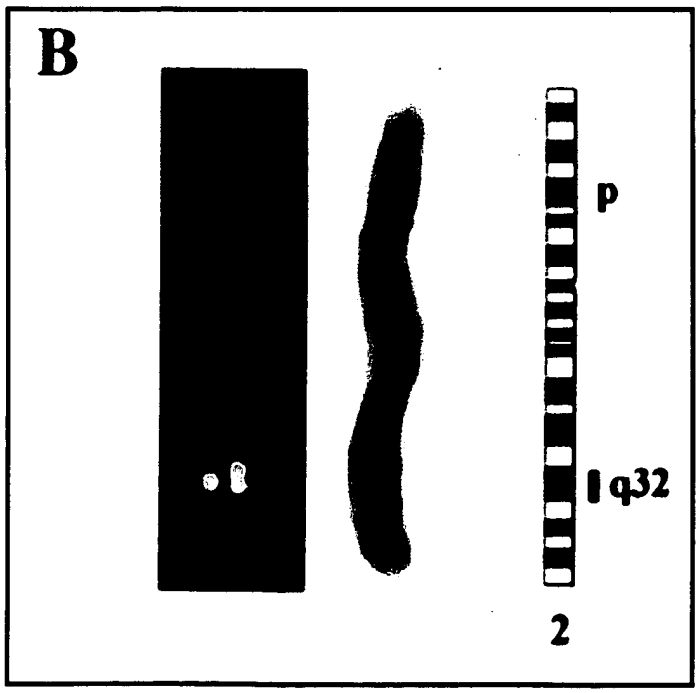

FIG. 7B

cDNA sequence of PCGEM1 Seq.ID No .1

```
AAGGCACTCT GGCACCCAGT TTTGGAACTG CAGTTTTAAA AGTCATAAAT TGAATGAAAA TGATAGCAAA   70
GGTGGAGGTT TTTAAAGAGC TATTTATAGG TCCCTGGACA GCATCTTTTT TCAATTAGGC AGCAACCTTT  140
TTGCCCTATG CCGTAACCTG TGTCTGCAAC TTCCTCTAAT TGGGAAATAG TTAAGCAGAT TCATAGAGCT  210
GAATGATAAA ATTGTACTAC GAGATGCACT GGGACTCAAC GTGACCTTAT CAAGTGAGCA GGCTTGGTGC  280
ATTTGACACT TCATGATATC AGCCAAAGTG GAACTAAAAA CAGCTCCTGG AAGAGGACTA TGACATCATC  350
AGGTTGGGAG TCTCCAGGGA CAGCGGACCC TTTGGAAAAG GACTAGAAAG TGTGAAATCT ATTAGTCTTC  420

GATATGAAAT TCTCTGTCTC TGTAAAAGCA TTTCATATTT ACAAGACACA GGCCTACTCC TAGGGCAGCA  490
AAAAGTGGCA ACAGGCAAGC AGAGGGAAAA GAGATCATGA GGCATTTCAG AGTGCACTGT CTTTTCATAT  560
ATTTCTCAAT GCCGTATGTT TGGTTTTATT TTGGCCAAGC ATAACAATCT GCTCAAGAAA AAAAAATCTG  630
GAGAAAACAA AGGTGCCTTT GCCAATGTTA TGTTTCTTTT TGACAAGCCC TGAGATTTCT GAGGGGAATT  700
CACATAAATG GGATCAGGTC ATTCATTTAC GTTGTGTGCA AATATGATTT AAAGATACAA CCTTTGCAGA  770
GAGCATGCTT TCCTAAGGGT AGGCACGTGG AGGACTAAGG GTAAAGCATT CTTCAAGATC AGTTAATCAA  840

GAAAGGTGCT CTTTGCATTC TGAAATGCCC TTGTTGCAAA TATTGGTTAT ATTGATTAAA TTTACACTTA  910
ATGGAAACAA CCTTTAACTT ACAGATGAAC AAACCCACAA AAGCAAAAAA TCAAAAGCCC TACCTATGAT  980
TTCATATTTT CTGTGTAACT GGATTAAAGG ATTCCTGCTT GCTTTTGGGC ATAAATGATA ATGGAATATT 1050
TCCAGGTATT GTTTAAAATG AGGGCCCATC TACAAATTCT TAGCAATACT TTGGATAATT CTAAAATTCA 1120
GCTGGACATT GTCTAATTGT TTTTTATATA CATCTTTGCT AGAATTTCAA ATTTTAAGTA TGTGAATTTA 1190
GTTAATTAGC TGTGCTGATC AATTCAAAAA CATTACTTTC CTAAATTTTA GACTATGAAG GTCATAAATT 1260

CAACAAATAT ATCTACACAT ACAATTATAG ATTGTTTTTC ATTATAATGT CTTCATCTTA ACAGAATTGT 1330
CTTTGTGATT GTTTTTAGAA AACTGAGAGT TTTAATTCAT AATTACTTGA TCAAAAAATT GTGGGAACAA 1400
TCCAGCATTA ATTGTATGTG ATTGTTTTTA TGTACATAAG GAGTCTTAAG CTTGGTGCCT TGAAGTCTTT 1470
TGTACTTAGT CCCATGTTTA AAATTACTAC TTTATATCTA AAGCATTTAT GTTTTTCAAT TCAATTTACA 1540
TGATGCTAAT TATGGCAATT ATAACAAATA TTAAAGATTT CGAAATAGAA AAAAAAAAAA AAA         1603
```

FIG. 8

cDNA sequence of PCGEM1 Seq. ID No .2

```
GCGGCCGCGT CGACGCAACT TCCTCTAATT GGGAAATAGT TAAGCAGATT CATAGAGCTG AATGATAAAA   70
TTGTACTTCG AGATGCACTG GGACTCAACG TGACCTTATC AAGTGAGATG GAGTCTTGCC CTGTCTCCAA  140
GGCTGGAGCC CAATGGTGTG ATCTTGGCTC ACTGCAACCT CCACCTCCCA GGTTCAAACG TTTCTCCTGC  210
CTCAGCCTCC CAAGTAACTG GGATTACAGC AGGCTTGGTG CATTTGACAC TTCATGATAT CAGCCAAAGT  280
GGAACTAAAA ACAGCTCCTG GAAGAGGACT ATGACATCAT CAGGTTGGGA GTCTCCAGGG ACAGCGGACC  350
CTTTGGAAAA GGACTAGAAA GTGTGAAATC TATTAGTCTT CGATATGAAA TTCTCTGTCT CCGTAAAAGC  420
ATTTCATATT TACAAGACAC AGGCCTACTC CTAGGGCAGC AAAAAGTGGC AACAGGCAAG CAGAGGGAAA  490
AGAGATCATG AGGCATTTCA GAGTGCACTG TCTTTTCATA TATTTCTCAA TGCCGTATGT TTGGTTTTAT  560
TTTGGCCAAG CATAACAATC TGCTCAAAAA AAAAAAATCT GGAGAAAACA AAGGTGCCTT TGCCAATGTT  630
ATGTTTCTTT TTGACAAGCC CTGAGATTTC TGAGGGGAAT TCACATAAAT GGGATCAGGT CATTCATTTA  700
CGTTGTGTGC AAATATGATT TAAAGATACA ACCTTTGCAG AGAGCATGCT TTCCTAAGGG TAGGCACGTG  770
GAGGACTAAG GGTAAAGCAT TCTTCAAGAT CAGTTAATCA AGAAAGGTGC TCTTTGCATT CTGAAATGCC  840
CTTGTTGCAA ATATTGGTTA TATTGATTAA ATTTACACTT AATGGAAACA ACCTTTAACT TACAGATGAA  910
CAAACCCCAC AAAAGCAAAA AATCAAAAGC CCTACCTATG ATTTCATATT TTCTGTGTAA CTGGATTAAA  980
GGATTCCTGC TTGCTTTTGG GCATAAATGA TAATGGAATA TTTCCAGGTA TTGTTTAAAA TGAGGGCCCA 1050
TCTACAAATT CTTAGCAATA CTTTGGATAA TTCTAAAATT CAGCTGGACA TTGTCTAATT GTTTTTTATA 1120
TACATCTTTG CTAGAATTTC AAATTTTAAG TATGTGAATT TAGTTAATTA GCTGTGCTGA TCAATTCAAA 1190
AACATTACTT TCCTAAATTT TAGACTATGA AGGTCATAAA TTCAACAAAT ATATCTACAC ATACAATTAT 1260
AGATTGTTTT TCATTATAAT GTCTTCATCT TAACAGAATT GTCTTTGTGA TTGTTTTTAG AAAACTGAGA 1330
GTTTTAATTC ATAATTACTT GATCAAAAAA TTGTGGGAAC AATCCAGCAT TAATTGTATG TGATTGTTTT 1400
TATGTACATA AGGAGTCTTA AGCTTGGTGC CTTGAAGTCT TTTGTACTTA GTCCCATGTT TAAAATTACT 1470
ACTTTATATC TAAAGCATTT ATGTTTTTCA ATTCAATTTA CATGATGCTA ATTATGGCAA TTATAACAAA 1540
TATTAAAGAT TTCGAAATAG AAAAAAAAAA AAAAATCTA                                   1579
```

FIG. 9

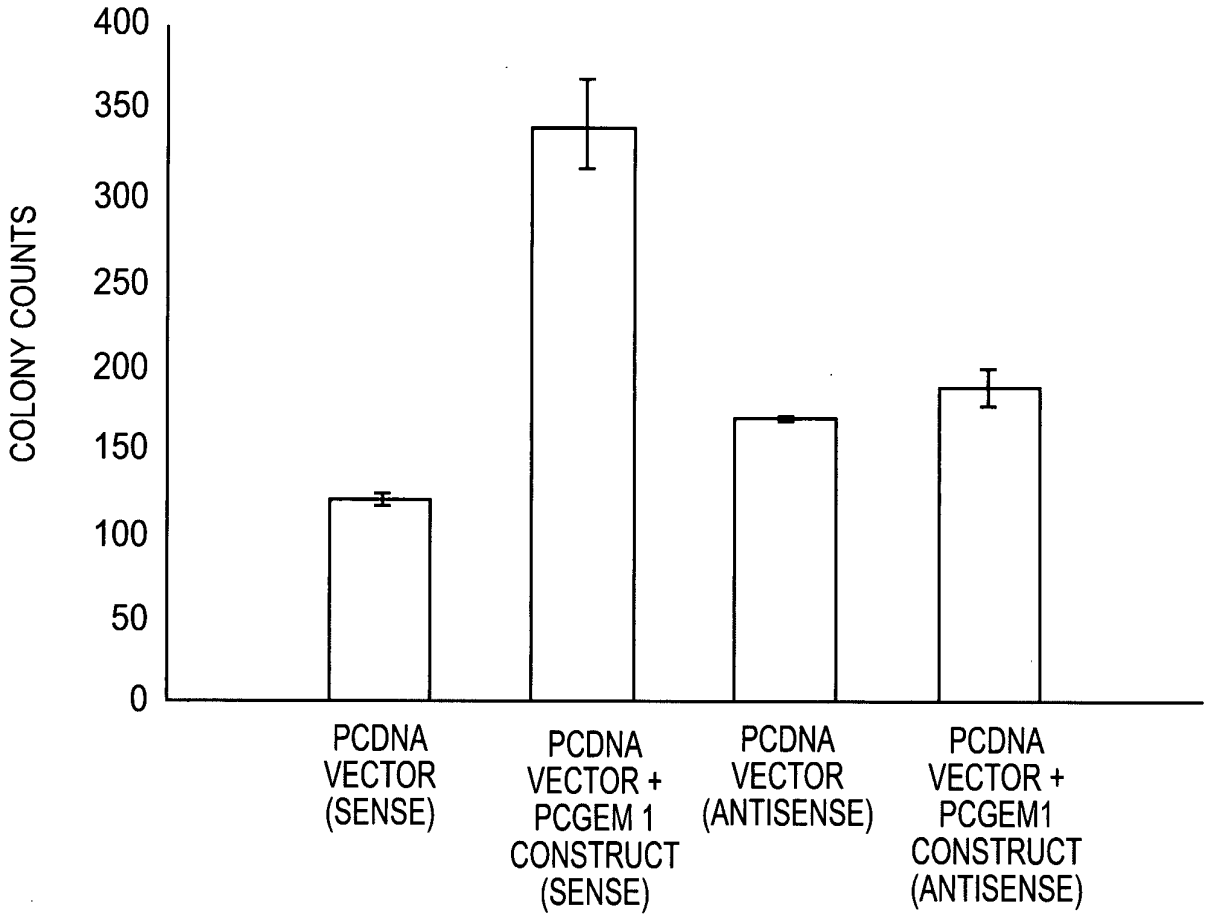
COLONY COUNTS
400
350
300
250
200
150
100
50
0
PCDNA VECTOR (SENSE)
PCDNA VECTOR + PCGEM 1 CONSTRUCT (SENSE)
PCDNA VECTOR (ANTISENSE)
PCDNA VECTOR + PCGEM1 CONSTRUCT (ANTISENSE)

FIG. 10

cDNA sequence of PCGEM1 Promoter Region Seq.ID No.3

```
TCCCTCTTGC GTTCTGCAAT TTCTGAAAAA AAGATGTTTA TTGCAAAGTG ATATGAGCAC TGGAAAGGTA  70
CTAATTCCAA TTTGATTCTA ATTGGATGAG TGACATGGGT AAGCGATTCT AAGCATTTGT GTTTTTTTTA 140
GTAGTATGGA ATTTAATTAG TTCTCAGTAT GTTAGTGAAG ATGAATGAAA ACATGCATAT GTTTCCATGT 210
ATTATAAATA TTTTAAAATG CAAAAAATTA TTCTAATGAA TATATAAATA TAAAGCATAA CAATAATAAT 280
ACAATACCAC CCATAAAGTC ATCATCTAAT TTAAAAACTA AAACATTAAC ACTTGAATCT CCCCCATTGC 350
AACATCTTTC CCGACTTGTG TGTTTTTTTC TTTTGCTTTT AAAATTTTTG TTTTATCATA TGTCTGCATA 420
AGATTATATA GCTTTCCTTG TTTTAAGCTT TTTAAATAAT ATATTGTAGT TATATTATTT GTGCTTTGCT 490
TTTTTTACTT AACATTATGG TTCTAAAATT CAGTAATGTG TTGGGCATGT ATAATTTGTT TATTTTTAAT 560
CTCTTTGACA TTCGACTATA TAAATTTCAG TTTGTTTATT GACTCCTTTG TCTATAGATA CTCTGCTATT 630
TCTGTTTTTG CTGTTACAAA AATAATGCTG TTTTAAATTT CATTTTGTAT ACTTTTTTGA GGCATGTGTA 700
TGAGTTATTC TAAGGTAAAA AAATAAGAAA AAATTGCTGG GTTATAAGAT TGTCACATGC TCGAATTTAC 770
AAGATAATGC CAAATCATTT TTCAAAGTAA TTATACCTAT TTATACTACC GGTATGAGTA TATTGGTGCC 840
CACATAGTTG CTTGTTCTGC CAAAGTTTGG TATGATCGAA CAATAATTTT TGCCCATCAA ATGGCATAAA 910
ATAAAATCTC AGTGTGCTTT TAATTTGCAT TTTCTATGTT TAAGAATTGT TTCTTTTTTA ACCATTTATA 980
ATTTACTTTT GCTGAAATGC TTGCTTATTA TTTTTGCTCC CCATTTTTTC CTATTGGATT GCTTTTCTCA 1050
TTAATTTATA AGAATTTTAT ATGGTTTAGA TACTAATTAT TATATTACTG AAAATACCTT TATCAGTTTG 1120
TTGTGTACTT TCTACTTTAT GTCTTGTGAT GGATAAAAGT TTTAAATTGT ATTGTGTTGA AGTTAACATT 1190
TTTAAATTTT ATAATCAGCA TCTTTAATAA TCTCTTTMTA AAATTTTCCT TTACATAGAT GTCATAAAGA 1260
TACATCTCTA TAATTTCTTA TTTTTTTGGC ATATGTTCAT TAAGTCATTT TATCATTTTT TAGTAATAAA 1330
TTGCAGTTAT TTATGAAACA AATAATTTTT AAAATTATAT ATGCTTTCTT TAAAAATTGA TCTTAGCATG 1400
CTTCACTATG AAGCTTGAGG CTTCACTGCA CGTTGTACTG AAATTATGTA TAAAACAGTG GTTCTGAAAA 1470
TCTCTGAGTT CATGACACCT TTAGTGTCTC AGGTTTTTTT GCTTTTGTTC TTGTTTTTTC TCACAAAGCA 1540
CCTAAGTTAA ATAAAAACAA AGCACAAAGC TATCAGCTTC ATGTATTAAG TAGTAAGCTC CCATGTTAAC 1610
AGTTGTAACT TGCCTGGTGC CCAATAGATG TCACTCTGTT TTCCTAGAAA CTTTAAAATA TCCCTCAGTG 1680
CTCCTGTTAA TTCATGGTAG TGCCCCAAGG CACTCTGGCA CCCAGTTTTG GAACTGCAGT TTTAAAAGTC 1750
ATAAATTGAA TGAAAATGAT AGCAAAGGTG GAGGTTTTTA AAGAGCTATT TATAGGTCCC TGGACAGCA  1819
```

FIG. 11

cDNA sequence of PCGEM1 PROBE Seq.ID No.4

```
TTTTTTCAAT TAGGCAGCAA CCTTTTTGCC CTATGCCGTA ACCTGTGTCT GCAACTTCCT CTAATTGGGA  70
AATAGTTAAG CAGATTCATA GAGCTGAATG ATAAAATTGT ACTACGAGAT GCACTGGGAC TCAACGTGAC 140
CTTATCAAGT GAGCAGGCTT GGTGCATTTG ACACTTCATG ATATCATCCA AAGTGGAACT AAAAACAGCT 210
CCTGGAAGAG GACTATGACA TCATCAGGTT GGGAGTCTCC AGGGACAGCG GACCCTTTGG AAAAGGACTA 280
GAAAGTGTGA AATCTATTAG TCTTCGATAT GAAATTCTCT GTCTCTGTAA AAGCATTTCA TATTTACAAG 350
ACACAGGCCT ACTCCTAGGG CAGCAAAAAG TGGCAACAGG CAAGCAGAGG GAAAAGAGAT CATGAGGCAT 420
TTCAGAGTGC ACTGTCTTTT CATATATTTC TCAATGCCGT ATGTTTGGTT TTATTTTGGC CAAGCATAAC 490
AATCTGCTCA AGAAAAAAAA ATCTGGAGAA AACAAAGGTG CCTTTGCCAA TGTTATGTTT CTTTTTGACA 560
AGCCCTGAGA TTTCTGAGGG GAATTCACAT AAATGGGATC AGGTCATTCA TTTACGTTGT GTGCAAATAT 630
GATTTAAAGA TACAACCTTT GCAGAGAGCA TGCTTTCCTA AGGGTAGGCA CGTGGAGGAC TAAGGGTAAA 700
GCATTCTTCA AGATCAGTTA ATCAAGAAAG GTGCTCTTTG CATTCTGAAA TGCCCTTGTT GCAAATATTG 770
GTTATATTGA TTAAATTTAC ACTTAATGGA AACAACCTTT AACTTACAGA TGAACAAACC CACAAAAGCA 840
AAAAATCAAA AGCCCTACCT ATGATTTCAT ATTTTCTGTG TAACTGGATT AAAGGATTCC TGCTTGCTTT 910
TGGGCATAAA TGATAATGGA ATATTTCCAG GTATTGTTTA AAATGAGGGC CCATCTACAA ATTCTTAGCA 980
ATACTTTGGA TAATTCTAAA ATTCAGCTGG ACATTGTCTA ATTGT                              1025
```

FIG. 12

PCGEM1 Primers Used for PCR

PCR PRIMER 1 (SEQ ID No.5)

Sense Primer 5' TGCCTCAGCCTCCCAAGTAAC 3'

PCR PRIMER 2 (SEQ ID No.6)

Antisense Primers 5' GGCCAAAATAAAACCAAACAT 3'

PCR PRIMER 3 (SEQ ID No.7)

Sense Primer 5' TGGCAACAGGCAAGCAGAG 3'

FIG. 13

Complete Genomic DNA sequence of PCGEM1 gene.

TCCCTCTTGCGTTCTGCAATTTCTGAAAAAAAGATGTTTATTGCAAAGTGATATGAGCACTGGAAAGGTACTAATTCCAA
TTTGATTCTAATTGGATGAGTGACATGGGTAAGCGATTCTAAGCATTTGTGTTTTTTTTAGTAGTATGGAATTTAATTAG
TTCTCAGTATGTTAGTGAAGATGAATGAAAACATGCATATGTTTCCATGTATTATAAATATTTTAAAATGCAAAAAATTA
TTCTAATGAATATATAAATATAAAGCATAACAATAATAATACAATACCACCCATAAAGTCATCATCTAATTTAAAAACTA
AAACATTAACACTTGAATCTCCCCCATTGCAACATCTTTCCCGACTTGTGTGTTTTTTTCTTTTGCTTTTAAAATTTTTG
TTTTATCATATGTCTGCATAAGATTATATAGCTTTCCTTGTTTTAAGCTTTTTAAATAATATATTGTAGTTATATTATTT
GTGCTTTGCTTTTTTTACTTAACATTATGGTTCTAAAATTCAGTAATGTGTTGGGCATGTATAATTTGTTTATTTTTAAT
CTCTTTGACATTCGACTATATAAATTTCAGTTTGTTTATTGACTCCTTTGTCTATACATACTCTGCTATTTCTGTTTTTG
CTGTTACAAAAATAATGCTGTTTTAAATTTCATTTTGTATACTTTTTTGAGGCATGTGTATGAGTTATTCTAAGGTAAAA
AAATAAGAAAAAATTGCTGGGTTATAAGATTGTCACATGCTCGAATTTACAAGATAATGCCAAATCATTTTTCAAAGTAA
TTATACCTATTTATACTACCGGTATGAGTATATTGGTGCCCACATAGTTGCTTGTTCTGCCAAAGTTTGGTATGATCGAA
CAATAATTTTTGCCCATCAAATGGCATAAAATAAAATCTCAGTGTGCTTTTAATTTGCATTTTCTATGTTTAAGAATTGT
TTCTTTTTTAACCATTTATAATTTACTTTTGCTGAAATGCTTGCTTATTATTTTTGCTCCCCATTTTTTCCTATTGGATT
GCTTTTCTCATTAATTTATAAGAATTTTATATGGTTTAGATACTAATTATTATATTACTGAAAATACCTTTATCAGTTTG
TTGTGTACTTTCTACTTTATGTCTTGTGATGGATAAAAGTTTTAAATTGTATTGTCTTGAAGTTAACATTTTTAAATTTT
ATAATCAGCATCTTTAATAATCTCTTTATAAAATTTTCCTTTACATAGATGTCATAAAGATACATCTCTATAATTTCTTA
TTTTTTTGGCATATGTTCATTAAGTCATTTTATCATTTTTTAGTAATAAATTGCAGTTATTTATGAAACAAATAATTTTT
AAAATTATATATGCTTTCTTTAAAAATTGATCTTAGCATGCTTCACTATGAAGCTTGAGGCTTCACTGCACGTTGTACTG
TTGTTTTTTGTCACAAAGCACCTAAGTTAAATAAAAACAAAGCACAAAGCTATCAGCTTCATGTATTAAGTAGTAAGCTC
CCATGTTAACAGTTGTAACTTGCCTGGTGCCCAATAGATGTCACTCTGTTTTCCTAGAAACTTTAAAATATCCCTCAGTG
CTCCTGTTAATTCATGGTAGTGCCCCAAGGCACTCTGGCACCCAGTTTTGGAACTGCAGTTTTAAAAGTCATAAATTGAA
TGAAAATGATAGCAAAGGTGGAGGTTTTTAAAGAGCTATTTATACCTCCCTGGACAGCATCTTTTTTCAATTAGGCAGCA
ACCTTTTTGCCTATGCCGTAACTGTGTCTGCACTTCCTCTAATTGGGGTGAGTAAGAGATTTTGTTATGTATATAATAGC
TAAGAATATAGTAATAATCCCTTAAATCATGGTTATTTTTAAACTACTAACATTTAGAAGACAAAATAAAAATGCTTTGA
AAAGTATAGAGGTTTTAGTGTAATTAGCAGGGAATAATGAAATGATTTGATAGGGCTACTCAGTTTTGTATAACTTTGGT
GCTTTAAGTCTGAATGCAGAGCATGGATGTTGTGATCCAGCCTTTATATGTTTTCCCTGAAGAAGATTTAATTTATTTGG
CCTTTTGAGAAACACATTTGGCATTGTAATATGTTTTGCTTCCAGGTTCTATCTCCAAGGATAATTTGACAAAATCACAC
ATAAATTTATTTTCAGGGCACACAGTTTCCCTTTTAGGGAACTCACAGAGGTAGAGAGTAATACAATAATCACATTTGAA
TATTCAGTAAGTGAGGTCCTCATAGATCTTATGTGTATGTCACCATGTATATAATTTTGTTAATCACTAGATGTATGAGA
CAAGAAATTTGAGGAATCTTAACTAGAGATTAAAATCAGGGATTTAAATCAAAGAAACATTTAAATGCCTCCTTTATTAT
TTAAATACCTGCATGGGAGAATCATTGAAAAAAAAATAAAAAGCATACAACTTGGGAATATTATAAACCAAGAAGAATTT
GTTATTCTGGTTGATTTTTTTTTCAGGCTCCGCACAGGCAACTTACCTTTATCTCTTTGTGATTTTTATTTCTTGTTAAA
ATATACAGAAATAGTTAAGCAGATTCATAGAGCTGAATATAAAATTTACTACGAGATGCACTGGGACTCAACGTGACCTT
ATCAAGTGACTTATCAGTGAGGTGAGCATTCTTAATTCAGATAATGGAACTTATTATCATAATCTTTTGCTTATGCTATT
GTTGAGCTTAACTACTTATTCATATTTGCATATGCATATTGAGATAATATCATTTCATTAATTTCAGTACTGAACACTAA
TCTCCTAAGAGTAATTGTGAAAGTTTCAGATTGCACTATTTTTTAACTATATATCTGTATGTTATCTTCATATATGCTTGA
ATAACTTATAAGCAATTGAAACTTTCAATTACAGTATACTATTGAAGCAAATCAACAAATATATACACATATCCATTAGC
AATAGTAGATAATTTTTGTAAATGTCCAGCACAGTTCTTCATATGTAGAGGATGTTCAAATTGGCTAAGTTCCTTTTCTC
TCTTAATTATTAGTATTTTTCCTACTGCTCTTTGTATAATTATTCCTTCCTCTTTAGCTCCAATCCTTACAATCTATTCT

FIG. 14

TAACATAGCAACTGGGAAGAAAGTTTTTAAACATAAACCAGATGATGTCACTCCACCCCACAAAACTTCCACTATTCTCT
GTCACACATAGAAAGAAAGAAAAAAAATATTGAAAACCTACAAAGACTTGCTATGATCTGGTCCAGGCTCTCCCTAAAAT
TTCATGTAATTTCCAGCCACTAGGCCTTTCTGGCTCTCCTTCAATCTCATTAGCCTTTTCACTACTACAAGTTAGACTGG
GTTTTGGCCGAGGTATTTCTTTTTTTCATATTTTGCCTTTGCCTAGATTGCTCTTCCAATAGATATTCACAATTGCATCA
TCATTTCTATATACGTGCTAAAAGGTTTCCTTGTCCAAAATAGCTTCAGTGACCACCTGATCTAGAATAGTCTCGATCAA
AAGTTTCTTTTCCTTTTCCTCACCACTTGATATTTATATCAAACATTTATTTGTGTAATTTATGTGTTTGTTTGTTTTCT
GTACTAGCATTATGATGACCATACTATTTGATGCCCCCCAAAAAATACTTTCGAGAATGACAGGGCAAAGCTAAAATAAT
TAAATTATATAATTTTGACATAGGCACTATTGACAAAAAGCAATTGATGTTATGATAGTGTTAGATCTATGAAATAGTAC
TATTTAAAAGTAATTCTCTGAAATACAATTTTCTAAAACTAAAAGCAGCATATGTACATGAAACACCAAAAAACTTCCTT
ATATTTATCACTGGAAGATTTAAAATAGTATAAGTAGTAACTTATTTAATATATTTTTGATTATTTAATTAATTTTATAG
TATCCAACTCTAATATAATGCCACTGGTATTTGTTCAAAATATTTTAATGTTGTCTATTTATTTTTAATTTGCCTAAAAA
TTATCTTAAATGAAAATTTTTGGTTAATAAATTTGAAAATACTGAAACCCTCATCTCCAGTCTCTGTGGATCCTAAAGTT
TTTAGTTGAGAAAATAATTTTTCTCTAGAGAATGAAGTAGCTTGTAAGCTTGGAGAAATTTCTGCTAAATAAATGATATT
ATCAACTCTTATTTTCTTCAATACGAAATATATAAATATTTCAGCTCATATATTTTTGCAGGTGCTATGCTTTTGCTTCC
AATCATAATTTCTGACAAATATTTTGGAAGTCAAAACTTGTCTTCTATTTTGTTATTTAAAATTATATAGACTACTTTTG
TAAACCTTTATACTATCAAATCATAGGCAATTTCAGTTTGATTTCATTCTGGTGCAGAATATAAGTTTATCCAAGTAAAA
CAGGAGTCACTTCAAAAGATTCCTCCCACTGACTGAGATATTCCAAAGCCAACTTTGCAAAATTTCAGAATTAAATATTA
TACTTCTTTGTACCTTCATTTTATTTGTTCAATTTTTCTTTGTGTTTGTAGAAAATTTTAATATTTTTCTGTTTTCAAGT
TTTGATTTTAATTTACTACTTTATAATTTTTAAAGGTAAGTTTTGTGAGGCTATATTCATTATGTGTTTTGAATAAAGAC
ATACAATTAATTTTGAGAACTGCAATAAAAATTATAAGACTATTAAAAATGCAGTAAGTGTACTACACTTAGGCTGCTAA
AAATGCAGTACCAGTAGACTACATTTAGGCTGCTTAAAGTTAGTTCTTCTAAGTACCATATACTTTAAAATTTTAGCTAA
TGATGGAGAACAAAGACAGAAAGACTGTGTTACCATATTCTAGTTGGCCATTTTGTTTTGTTTTGAGAGACGTCACATCA
GCCTTATCATAAAAATTATTTGGTTTTACCATTTTGACTGTGAGCAAAATATACAGCATAATATACAAAATAAAATACAT
GTACATCTTCACAACTTCTTGTTTAGGATGCAATTATATATATATATATATATATATTTATTATTATACTTTAAGTTCTA
GGGTACATGGCACCACGTGCAGGTTGTTACATATGTATACATGTGCCATGTTGGTGTGCTGCACCCATTAACTCGTCATT
TACATTAGGTGTATCTCCTAATGCTATCCCTCCCCTCTCTCCCCACCCCACAACAAGCCCCGGTGTGTGATGTTCCCCTT
CCTGTGTCCATGTGTTCTCATTGTTCAATTCCCACCTATGAGTGAGAACACGCAGTGTTTGCTTTTTTGTCCTTGCAATA
GTTTGCTGAGAATGATGGTTTCCAGCTTCATCCATGTCCCTACAAAGGACATGAACTCATCATTTTTTATGGCTGCATAG
TATTCCATGGTGTATATGTGCCACCATTTTCTTAATCCGAGTCTGTCCATTGTTGTTGGACATTTGGGTTGCAATTTTGA
GTTTCATGTGTAGCATGTATAGCACAACCAATTAAGATTTCTTTCTTTCTCTCTTTTTTTTTTTTTTTTGTTGAAATGGA
GTCTTGCCTGTCTCCAAGGCTGGAGCCCAATGGTGTGATCTTGGCTTACTGCAACCTCCACCTCCCGGGTTCAAGCGATT
CTCCTGCCTCAGCCATCCGAGTAGCTGGGACTATAGGCGTGCACCACCATGCCCAGCTAATTTTTGTATTTTTAGTACAG
ACGGGGTTTCACCACGGTGGCCAGGATGGTCTCAATTTCTTGACCTCATGATTCACCCGCCTTGGCCTCCCAAAGTGCTG
GGATTACAGGTGTGAACCACCAAGCCCGGCCTGTCACAAGTTTTTAGTGTTCTATTTTAATACAGAAATTAGATAAATCC
AAAGAGAAAGACATTTCATATGTGCGTAGAGTTGTCGGAAGAAATGAGAGTCTTATAAATAACTTTAAAAATTGTGAAGA
AATAAAGGCAAAATAGTCCTATGCAGTTTGATTTAAATATATTCTTAATAAGAGCTACTTTTGTGAAACCAGAATAATTG
AAACATGTAGATATGGATCTTCATTAGTGACTGACATAATATATTGTTATTGTTACTATTTTATTGTATCAGCCAACTAA
TATTGAGTGCTTTGTGTATCCTAAGCACTATGCTAAACACTGTACCAGTATTACCTGATATAATCATATTAATATTTATT

FIG. 14(cont'd-1)

ATTTCACTTTTCATATGAAAAAATTGAAGCACAGATTAAGACACTCCGAAATCATACCTCTATTGATTATCAGCACCAGG
ATTTGAATTGAGGCACTCTGATCCAGAGAAGCTTTTGTTTCCATGAAGGCTTATGTTGGGGAAAAATAATCAAATTGCCT
GTACCTCAGTTGTATAAATAAGAGGTTGGGTTGGTAGATGATTCTGGCTGATTCAGCAGAAAAGAAATTTATTCAAAGGA
TATCACACAGTTTTCATAACAGTTAAGAATACAGAGGAAACAGGGCACCAGGGCTAAGTACAGACCAAAGTCCAAAACCA
CTGCCAAAGTTGCAGCAAGGAGAACAGCACAAATTTGCTTGCTGTCACCCGCCACTAGATGCTTTTGTTTGGAGCCTTGA
ACTTGACTTACACTGCCACTGACATCAGCACCAGTGCTCTCTGTGTACTAGGAGGTGGAGTTGGTGACGTTGCTGAACTA
AAAGCAGATGTTTCTGCTGTGAAATAGATACCTAATACAGAACCTGATTCCTCATTCATTCCCTCCCCAAATCATATGCT
TGTAGTGTGGCTAGAGTTTCTGTTTCTCCTTGGTCCAGGCAGAATTTATGAAGCTTGCTATTTATCGCCTTAAAGATTAG
AAGAATATTCATAAGGTATTAGATTGCCATAAGGTTGAACAAATCAACATTCAACTTCAAGGATTCAACATTGTTTTGTT
TTCTTTTGGGATACCTCTGCAGCAGTTCAAATCTTATTTCTGCCCTTGGACAACCAGGTTTATAAATATTGCAGATTCTC
CACTGACTGCTTTGATCCTATCTTCTATATTTATGTATACTAATTAGCATATAATAAAAGATTATGTTACAGAATCTCAA
AATTAGTAATTATGAATTGAGATGGTGTTATACAGTACACTAACATCCAAGAGACTTGTTTATTCCAAGGAAAATATTTA
GAGATATTAAATGATATTTCTCATCCTTTAGACATATACATTTTTTAGCTTACAGCCTGCTTTAGGCAAGCAACAGACTC
TCAGGATCTGCTCCTACCAGGGTCTGAACATTTCCTCCCAGTTTTAAAGAAACAAATTCAAATAACATTGTAACCTCCAG
AGGAAAGTTCAAGGTCTTTTATAGTATTGTTTAAACAGTACAGCTGAGGAAACTAAAGACAGAGAAGTTAAATGCCTTGG
CACTTAGTCTAGATTTACAATAAACTCCTYTCTACTTAGGACCCACTAACAGGGGCTGCATTTACACCAAAACCATGAAG
GTGGCCCAAGTCATCACTGAGAAGTAGTACAAGCACCGAGGGAATGACTTCAACAGGAACAAGAAAGCGTGGAAGGAGAT
CCTAGCAGGAAGCTCCACAAGAAGATAGCATGTTACGTCTTGCATTGGATGAAGCAGGTTCAGAGAGACCTAGTGACAGC
TATCTCCGTCAAGGTGCAGAAGGAGAGATCATTGAATGTAGCATTTTCATGCAAAAAAAAAAATGTTGAAGTCTTTGGAC
TTCGGGAGTCTGTCCAAACTGCAGGTCACTCAGCCTACAGTTGGGATGAATTTCAAAACACCAGTTGGAGCCGGTTGAAT
CTTTCTGCTATGCTGTAATATTTTCAGTAAACCCAGCGCAACAACAACAACAAAACACAAAAGGAGGAGAAGCAGCCAAG
TCTCTTGGTTTACAGAGTAGCTCCTAATACCCCTTGCTGTCTGTCTCAAGTGCCCAATGGGAAGATAGTCAAAACAATAT
TCACACCTGTGATTCATCTCTCTACATGCAGTGTGTGTGAATCTTTATATACTGCATATTAAGGATCTGTCTTTACAGAT
AAAAACTAAAGCATTGAAGGAACTCCTTGTTTTGACTTATCAAAGTCCTTAAGAAAATACTAGAAAATTATAGCCATTGT
TTCAAATTTTAGCTTTATATTATCACTTGAAATGTGATGAAATGTGGCTGATAGATAATAATTCACTGATAACCTACAGA
CAATTCCCATCTTAAAATGGACCATTGGATTGAAGAATTAAATAAAATTGAGGGTTTTCCTTACATGTTTTGTCTAAAGA
GCGAAGTAGAAACAACTGTTCATAGATCTTCATTGAGGATTCGCATGTGAAGTAAGTACTCCTAACATAAACAAGTGGAC
TTATCAACCAAGTTCCATAAATCATGAACAAAAATATTTGTCCCCAGAGAGACTATTTTTCCACCACATCTCTTGTAATA
AACACAGAGCCCAGTTCAGTTAAAATACTTTAAGGGTGGACGGTTCAGGGCCTGCTGAGTGGCACTCAGTAAGAAAACCC
AGCAGAACATTTACTTCTCTCTTTATTCCAGAGCATCAATGGCCAAGGCTGGAAGATCCCAGAACACTGAACAGACATTT
GGTCTCTTATGGCCTGCCAATTTTCACAGTGGGTTCCAACGCTTTGGGTCAAACCAAAATAGACCTGTTAGAAAAATGTC
GGTTGGAATACGCTAACAATAAGACAGAATAAATGTGATTATTTCACCTCATTTTTATAGGACTTGAGTAATTTTATTAT
AACATTCTTGAGGGCTGGAAAATCTGAATGTTAGGACACCAAATATCTCCAGAAAACAAGTTTTATATTTCTAATCCTGC
ATAATAAACCTGGGGCCACTGCAGGCCTCATTAATAAAAACCTAATGGTATAACAATAATGAGGAGGAAATGCCAATGCC
GCACAAATCTGTTGAGACTAAAATATTTCTCACCCCAGCAGGCTTGGTGCATTTGACACTTCATGATATCAGCCAAAGTG
GAACTAAAAACAGCTCCTGGAAGAGGACTATGACATCATCAGGTTGGGAGTCTCCAGGGACAGCGGACCCTTTGGAAAAG
GACTAGAAAGTGTGAAATCTATTAGTCTTCGATATGAAATTCTCTGTCTCTGTCAAAAGCATTTCATATTTACAAGACAC
AGGCCTACTCCTAGGGCAGCAAAAAGTGGCAACAGGCAAGCAGAGGGAAAAGAGATCATGAGGCATTTCAGAGTGCACTG

FIG. 14(cont'd-2)

TCTTTTCATATATTTCTCAATGCCGTATGTTTGGTTTTATTTTGGCCAAGCATAACAATCTGCTCAAGAAAAAAAAATCT
GGAGAAAACAAAGGTGCCTTTGCCAATGTTATGTTTCTTTTTGACAAGCCCTGAGATTTCTGAGGGGAATTCACATAAAT
GGGATCAGGTCATTCATTTACGTTGTGTGCAAATATGATTTAAAGATACAACCTTTGCAGAGAGCATGCTTTCCTAAGGG
TAGGCACGTGGAGGACTAAGGGTAAAGCATTCTTCAAGAATCAGTTAATCAAAGAAAGGTGCTCTTTGCATTCTGAAATG
CCCTTGTTGCAAATATTGGTTATATTGATTAAATTTACACTTAATGGAAACAACCTTTAACTTACAGATGAACAAACCCA
CAAAAGCAAAAAAGCAAAAGCCCGACCTATGATTTCATATTTTCTGTGTAACTGGATTAAAGGATTCCTGCTTGCTTTTG
GGCATAAATGATAATGGAATATTTCCAGGTATTGTTTAAAATGAGGGCCCATCTACAAATTCTTAGCAATACTTTGGATA
ATTCTAAAATTCAGCTGGACATTGTCTAATTGTTTTTTATATACATCTTTGCTAGAATTTCAAATTTTAAGTATGTGAAT
TTAGTTAATTAGCTGTGCTGATCAATTCAAAAACATTACTTTCCTAAATTTTAGACTATGAAGGTCATAAATTCAACAAA
TATATCTACACATACAATTATAGATTGTTTTTCATTATAATGTCTTCATCTTAACAGAATTGTCTTTGTGATTGTTTTTA
GAAAACTGAGAGTTTTAATTCATAATTACGTTGATCAAAAAATTGTGGGAACAATCCAGCATTAATTGTATGTGATTGTT
TTTATGTACATAAGGAGTCTTAAGCTTGGTGCCTTGAAGTCTTTTGTACTTAGTCCCATGTTTAAAATTACTACTTTATA
TCTAAAGCATTTATGTTTTTCAATTCAATTTACATGATGCTAATTATGGCAATTATAACAAATATTAAAGATTTCGAAAT
AGAATATGTGAATTGTTCACCATACATAGAAATGAAAAGTTCATTTCGTAAAGCAAGATGCTGGGTGAAAGAGTGCTTTT
GATTGAAAGATCACTAGATTAGTAGAGGGCAAGACTTTTAGTCCCTAATCTACCCTTAATAGCCATGTGGTCACGTGTAA
GTCAGTGAACCCATCTCATTCTCCTCATACTTTTTTCATCTCTAAAATGAGGGTATAATTTAAGCTCGTTCATTTTTTTT
TTTTTTTGAGATAGAGTTTTGCTCTTGTCACCCAGGTTGGAGTGCAATGGCACGATCTCAGCTCACTGCAACCCTCTGCT
TCCTCGGTTCAAGTGATTCTCCCTGCTTCAGCCTCCCAAGTGAGCCCGGGATTACAGGTGCCCGCCACCACATCTGGGCC
TAGATTTTTTGTATTTTCACCATGTTGGCCAGGCTGGTCTCGAACCCCTACCTCAGGTGATCCCTCGCCTCGGCCTCTCA
AAGTGCTGGGATTACAGGTGTGAGCCACCACGCCCAGCCCAATATCAGTTTTTCTTTTTTAACACAAGGCTAACACAATC
AAAATACTAGCTAGGGGAGAAAAAAAAAAATAAGGCACTGTTTATGTGTAACAGGCTCTTGTTGCAATCCACTGGGGCAGA
CCAAATAAACAGTAAGAATCAAATCCTTTTCATATAATCCTTTCTTTGCAGAATACATAAAATCCCCACAAATGGCTTAT
CTTCCTTTTTATGATATGTTGGAGAATTGTAGCTAAGTGACAGATATTTTGCTTGGGTGTATAGACCACAAAGGACTGTG
TCTTGATGATGGTTTGCATAAAATTATACCTTAGTTTTTACTTTGTATGTTACATGTTAGATTTAGAGTATGAAAATTAG
TAGGGAGGATTATTAACAAAGAACAGGGCAAGAGGAGTAGAATTAAACCTCTTCTAATACCTGTGCACAAGTAGGCTTTT
CAGAAACTCTACAACCCCAACATAAACTGGATAGTTAGAAAAGCACACTCCCAAGGAAGGCGGTTATGTTTTGCAGTTTG
AATCAGAAGAATAGAGCTATAGCAATCTTCATTCTATAGTAACATTAAAGAGCCTGGTTTATATTATAGCAGTCATTAAG
ATTTAAAAATTTACATCTTGCCGTTCTTCTTACTCACAGATTTTCGAGAGGTAATGTAATGATCACACGAGGTGAGAATC
ACTGCCTTTTATAATGCGATTAAATGCATGAACAAAGTTTCCAACAAATAACAGTAATAAAAAGAAACATGTATTAGCAC
TTAATAAGCCAGGTGCTGTACGACGTGTGTTACATGCTTTCAATCCATGAACTGGTAAACTGGTACTAGTATCTCTATTG
GACATGTGAGGAAACCAAATGGAGTTGATAAACAGTAGAGTTAAAAATTACTCTTCATATATTATATTGCCTCAATCTCA
CAGACATCTCTGCTACCAAAAGCTATCATATCTAGACTCGA

FIG. 14(cont'd-3)

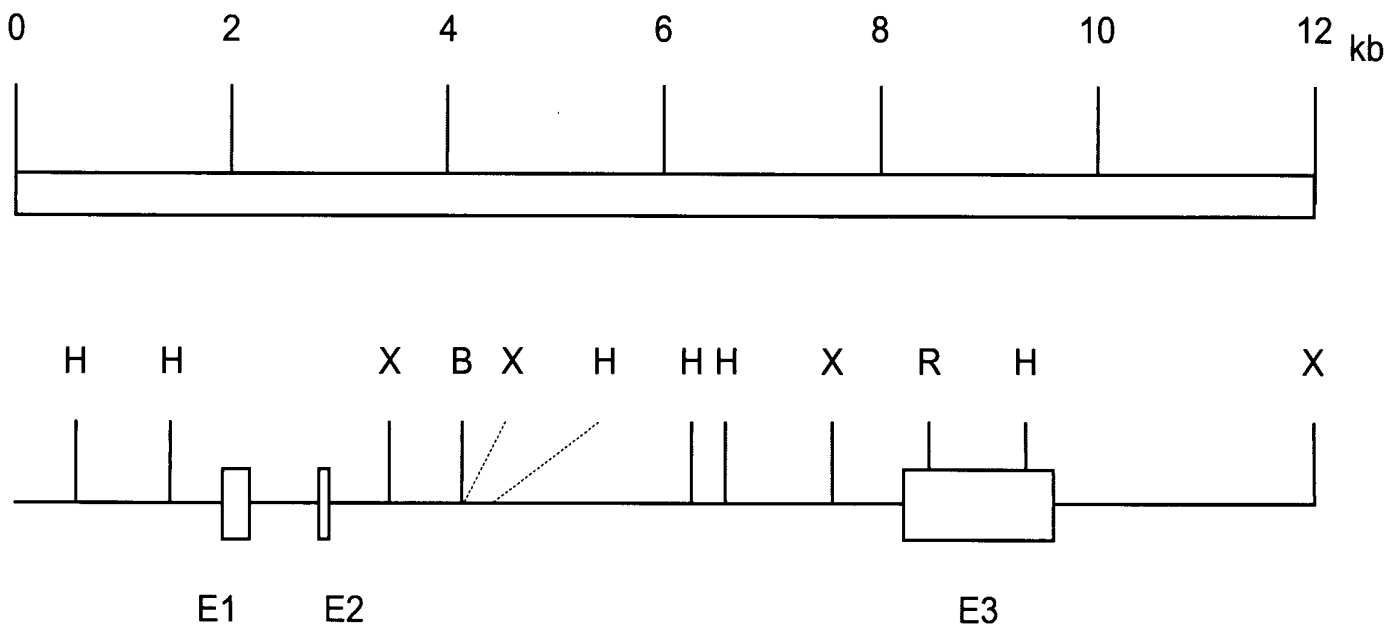

FIG. 15

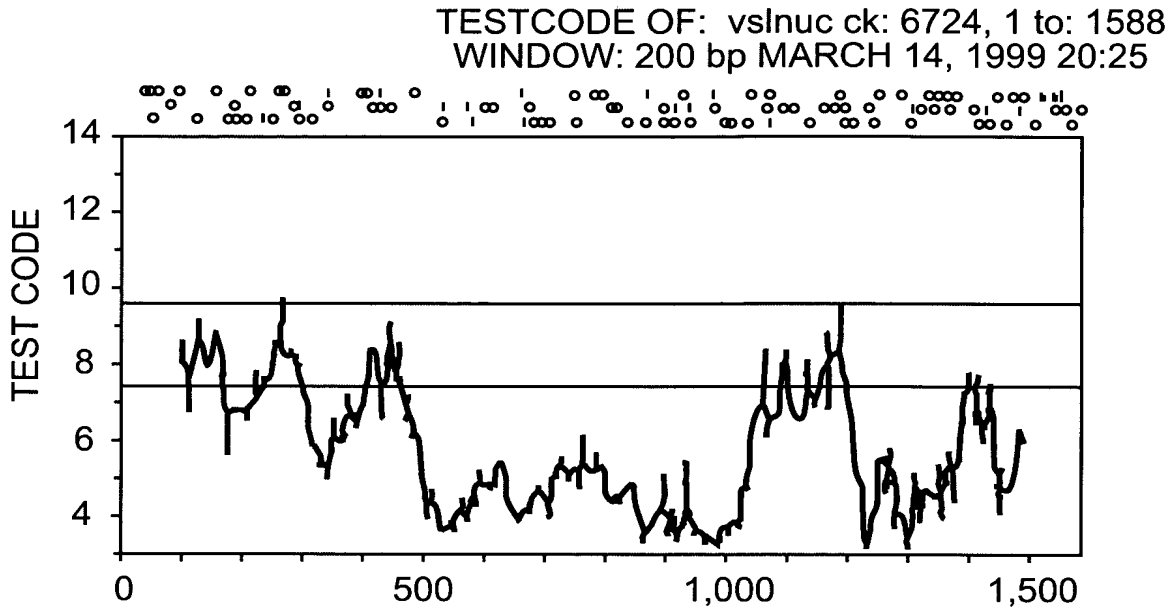

FIG. 16A

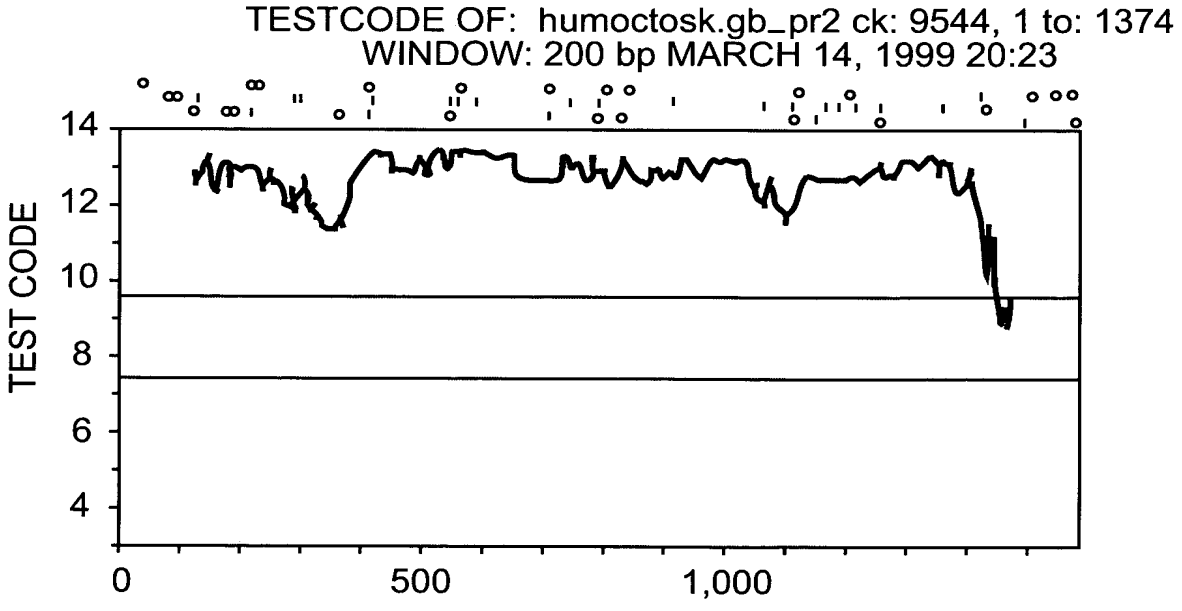

FIG. 16B

FIG. 17